CSF inflammatory response after intraventricular hemorrhage

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ABSTRACT

Objective: To investigate the temporal pattern and relevant associations of CSF inflammatory measures after intraventricular hemorrhage (IVH).

Methods: We analyzed prospectively collected CSF cell counts and protein and glucose levels from participants in the Clot Lysis Evaluation of Accelerated Resolution of IVH phase III (CLEAR III) trial. Corrected leukocyte count and cell index were calculated to adjust for CSF leukocytes attributable to circulating blood. Data were chronologically plotted. CSF inflammatory measures (daily, mean, median, maximum, and cases with highest quartile response) were correlated with initial IVH volume, IVH clearance rate, thrombolytic treatment, bacterial infection, and adjudicated clinical outcome at 30 and 180 days.

Results: A total of 11,376 data points of CSF results from 464 trial participants were analyzed. Measures of CSF inflammatory response evolved during the resolution of IVH. This was significantly more pronounced with initial IVH volume exceeding 20 mL. Intraventricular alteplase was associated with a significantly augmented inflammatory response compared to saline, even after correcting for initial IVH volume. There was an association but nonpredictive correlation of CSF inflammation measures with culture-positive CSF bacterial infection. None of the CSF inflammatory measures, including cases with upper quartile inflammatory response, was associated with a significant detrimental effect on 30 or 180 days functional outcome or mortality after multivariate adjustment for measures of disease severity.

Conclusions: Aseptic CSF inflammation after IVH is primarily dependent on the volume of initial bleed. Thrombolysis intensifies the inflammatory response, with no apparent detrimental effect on clinical outcome.

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GLOSSARY

CI = cell index; **CLEAR III** = Clot Lysis: Evaluation of Accelerated Resolution in IVH phase III trial; **cWBC** = corrected white blood cells; **eotIVH** = end-of-treatment intraventricular hemorrhage volume; **EVD** = external ventricular drain; **GCS** = Glasgow Coma Scale; **GEE** = generalized estimating equation; **GLM** = general linear model; **ICH** = intracerebral hemorrhage; **iIVH** = initial intraventricular hemorrhage; **IVH** = intraventricular hemorrhage; **mRS** = modified Rankin Scale; **RBC** = red blood cell; **WBC** = white blood cell.

Intraventricular hemorrhage (IVH) commonly results in mortality and poor functional outcome.[1–6] Experimental and clinical studies have demonstrated a CSF inflammatory response in association with IVH, reflected by changes in cell counts and protein and glucose levels.[7–10] The expected time course of these changes and their relationship to the volume of hemorrhage are not known, nor is how IVH may influence CSF inflammatory measures in the setting of bacterial infection.[11] With the advent of intraventricular thrombolysis aimed at enhancing clearance of IVH, there have been conflicting reports about the effect of this therapy on inflammatory response.[7,9,12–18] These studies were limited by cohort size, patient selection, or

Supplemental data at Neurology.org

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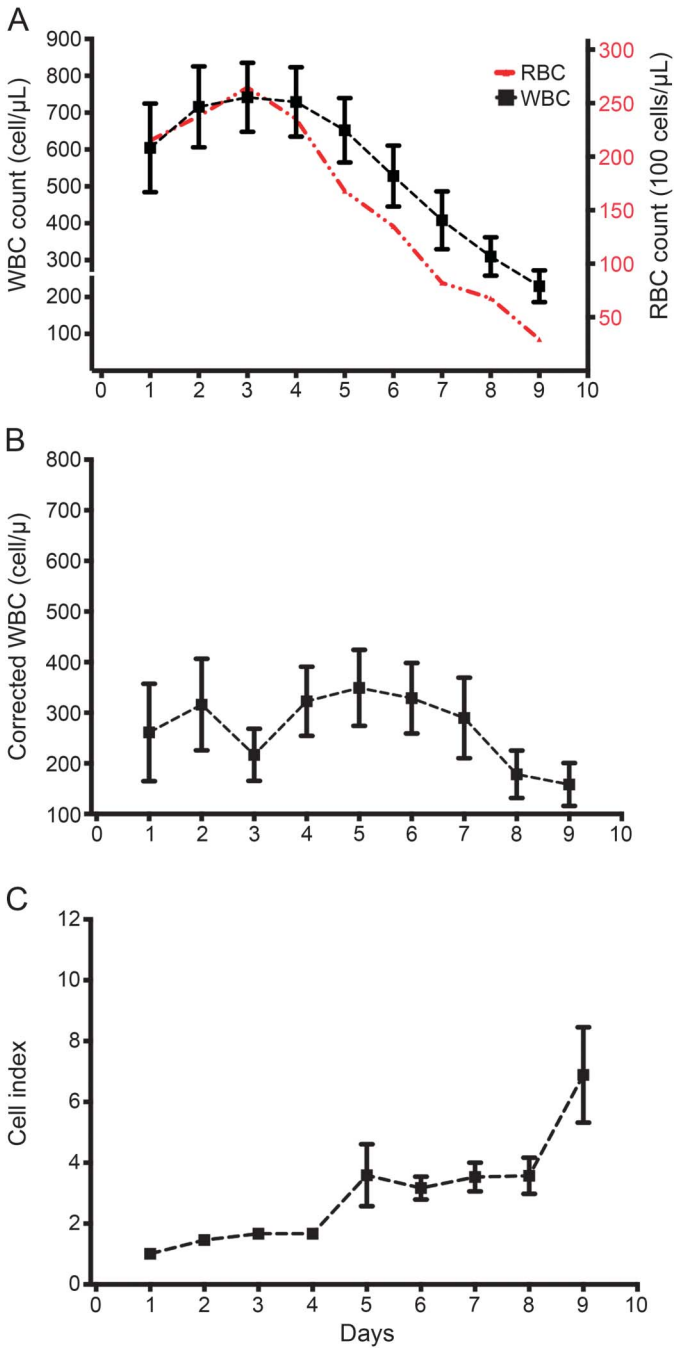
Figure 1 General patterns



Overall patterns (mean ± SE) for the trends of (A) white blood cells (WBC), (B) corrected WBC, and (C) cell index during the resolution of IVH over days 1–9 postictus. RBC = red blood cell.

follow-up, and none controlled for IVH volume or considered the potential effect of CSF inflammatory response on clinical outcome.

The recently concluded Clot Lysis: Evaluation of Accelerated Resolution in IVH phase III trial (CLEAR III)[19] provided a unique opportunity to study the classic measures of CSF inflammatory response in the largest prospectively enrolled patient series with IVH assembled to date. We hypothesized that intraventricular CSF cell counts and protein and glucose levels reflect an inflammatory response in the days following IVH, that this response is greater in cases with higher volumes of initial IVH (iIVH), and that this may correlate with thrombolytic treatment, IVH clearance, or bacterial infection. We examined any potential effect of CSF inflammatory response on mortality and functional outcome.

METHODS

Standard protocol approvals, registrations, and patient consents. This is a prospective observational cohort study of collected CSF laboratory results from patients enrolled in the CLEAR III trial (clinicaltrials.gov registration identifier NCT00784134). The respective participating sites had approval from their institutional review boards and the data handling was conducted in compliance with the Health Insurance Portability and Accountability Act.

Participants, treatment rendered, and CSF data collection and processing. Treatment rendered, demographic characteristics, and disease severity measures of trial participants were reported with the primary results of CLEAR III,[19] and are summarized in table e-1 at Neurology.org.

Enrolled participants had an IVH with obstruction of the third or fourth ventricle and associated intracerebral hemorrhage (ICH) volume less than 30 mL pragmatically treated with external ventricular drain (EVD) per local practice guidelines. Patients with underlying vascular etiology or uncorrected coagulopathy were excluded. As per protocol, enrolled patients had daily CSF samples collected from the EVD, and were analyzed for cell count, protein, and glucose during at least the first 7 consecutive days following randomization. Gram staining and cultures were added if bacterial infection was clinically suspected. CSF white blood cell (WBC) and red blood cell (RBC) counts (cells/μL), protein and glucose levels (mg/μL), and culture results were extracted from source records uploaded prospectively through the trial's secure electronic data capture system, along with peripheral blood WBC and RBC counts (10^3 cells/μL and 10^6 cells/μL, respectively).

Missing data points were not estimated except for peripheral RBCs and WBCs, where the value from an adjacent day was used if available. Participants with no recorded CSF results throughout days 0–10 were excluded (n = 36 of 500 enrolled participants). Hence laboratory CSF and peripheral blood results from 464 IVH participants in CLEAR III were studied.

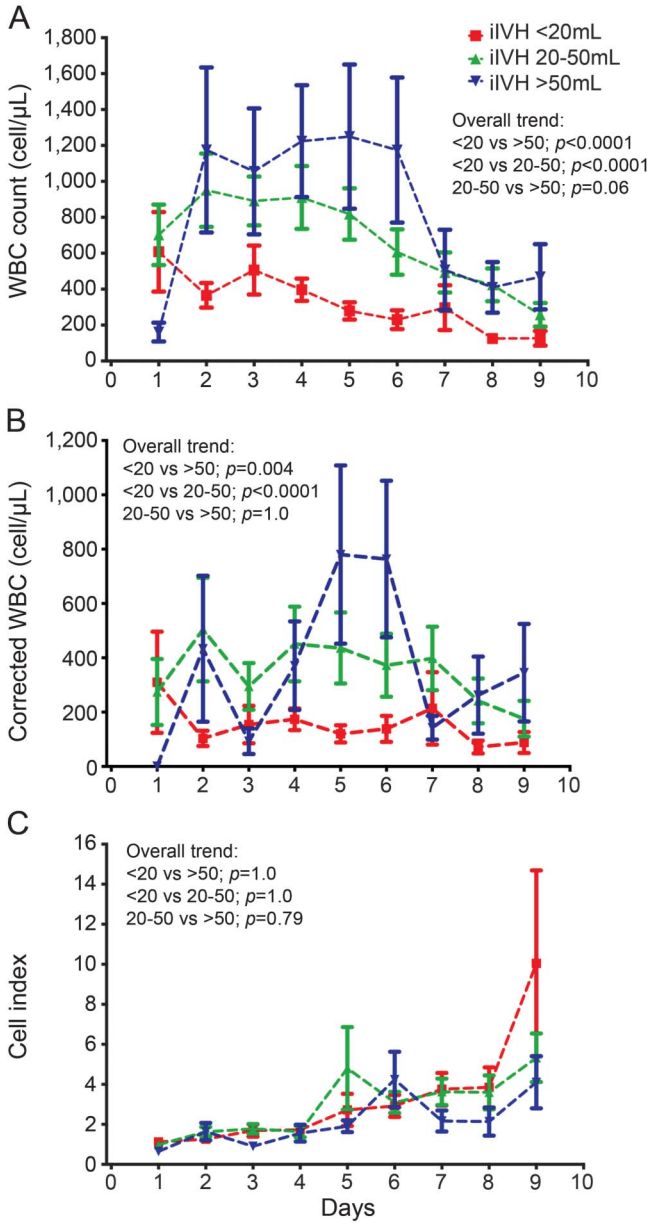
Two additional measures, corrected WBCs (cWBC) and cell index (CI), were calculated based on the relative abundance of RBCs and WBCs in peripheral blood samples of the same (or adjacent) day.[20–24] The 2 inflammatory surrogates were calculated per previously reported formulae.

$$\text{cWBCs} = \text{Observed} - \text{Predicted}$$

$$\text{CI} = \text{Observed}/\text{Predicted}$$

where observed = CSF WBCs, predicted = CSF RBCs × peripheral WBCs × 10^3/peripheral RBCs × 10^6. Negative cWBC data points (observed < predicted), denoting weak or absent inflammatory response, were counted as 0 for analysis. A CI > 1 indicated relatively higher WBCs in CSF than in the peripheral blood, and <1 indicated the converse.

Figure 2 Association of initial intraventricular hemorrhage (iIVH) volume



Temporal trend of white blood cells (WBC), corrected WBC, and cell index in the 3 prearticulated iIVH volume strata (<20 mL, n = 201; 20–50 mL, n = 120; and >50 mL, n = 54) over days 1–9 postictus. The *p* values listed with each panel refer to the difference in overall trend for the respective measure.

Sequential daily CSF values for each participant were tracked in relation to the date of symptom onset of hemorrhagic stroke, designated as day 0. Results were available from day 0 to day 10 from ictus in varying frequencies. With least missing values on day 1 through day 9, these were selected for analysis. With more than half of participants missing CSF WBC differential, neutrophil/monocyte ratio was therefore not considered in our analyses.

For each laboratory measure, the daily mean and SD were calculated across the whole sample to distinguish outlier values exceeding ±2.5 SDs. Each statistical outlier was individually evaluated against the participant's own values at the days immediately preceding and following. Statistical outliers that were out of trend for the participant (42 data points) were deemed erroneous readings and were excluded. Table e-2 summarizes the 11,376 data points ultimately included in our analysis. Cases with many missing CSF values (<5 readings over days 0–10, n = 203) had no difference in demographic and disease measures in comparison to those with more complete CSF datasets (table e-3).

Assessment of IVH volume, IVH clearance, bacterial infection, and outcome. To optimize accuracy and minimize bias, all IVH volumes were centrally measured from CT scans during the course of the trial at the trial's core image reading center using semiautomated segmentation and Hounsfield thresholds.[19] Initial iIVH was determined at the last CT scan prior to randomization. Cases were categorized into iIVH strata <20, 20–50, and >50 mL as prespecified in the CLEAR III data analysis plan. End-of-treatment IVH volume (eotIVH) was measured 24 hours after the last dose of study agent (alteplase or saline). This was used to estimate IVH clearance, calculated as (iIVH − eotIVH/iIVH). Treatment received was defined as placebo (saline injections 3 times daily, n = 251) or thrombolytic agent (alteplase at similar frequency, n = 249) administered through the EVD for up to 12 doses, until a protocol-specified endpoint of third or fourth ventricular clearance, or >80% clearance of IVH volume. Bacterial infection was strictly defined, for the purpose of this study, as a positive culture from CSF during the sampling protocol or within the first month from enrollment, as reported by the site and verified in the source documents. Outcome assessments by modified Rankin Scale (mRS) at 30 and 180 days after symptom onset were independently adjudicated by the trial's outcomes center at the University of Glasgow, Scotland. Functional outcome was dichotomized as good (mRS = 0–3), poor (mRS = 4–6), or mortality (mRS = 6), as prespecified in the trial.

Statistical analyses. Pearson correlation coefficients were calculated to evaluate the association between iIVH and IVH clearance rates and the CSF inflammatory measures on each day, and with mean, median, and maximum values for each measure. General linear models (GLMs) were used for assessments on the CSF inflammatory variables on a day-by-day analysis and overall period of 9 days. Mean, median, and maximum values of the variables were also modeled based upon the GLM. Bonferroni correction was used for adjustment of *p* value in analysis of the 3 iIVH volume strata.

Modeling the functional outcome utilized the generalized estimating equation (GEE) method for the repeated measurements of WBC, cWBC, CI, protein, and glucose. The model considered effect of iIVH volume (3 groups: <20, 20–50, and ≥50 mL), treatment rendered (alteplase and saline), as well as bacterial infection (yes and no). A variance–covariance structure of exchangeable correlation for repeated measures was used to account for the within-participant correlations. The same analysis was carried out for correlation between daily, mean, median, and maximum values of respective measures and poor functional outcome or mortality, adjusted for clinical variables (iIVH volume, IVH clearance, ICH volume, ICH location, and Glasgow Coma Scale [GCS]).

For analysis of the highest inflammatory response, participants were subdivided into 2 groups using the highest quartile of each CSF inflammation marker (WBC, cWBC, and CI). Multivariate GEE models were then conducted to compare the functional outcome (good vs poor) and mortality between the participants with highest inflammatory response (25% of all relevant participants) and the rest of the participants. Descriptive statistics such as mean, 95% confidence interval of the mean, median, interquartile range, and percentages were calculated to

Table 1 Association of initial intraventricular hemorrhage (IVH) volume and IVH clearance with CSF white blood cell (WBC) counts, corrected WBC (cWBC), and cell index (days 1–9, mean, median, and maximum)

	WBC				cWBC				Cell index			
	Initial volume		IVH clearance		Initial volume		IVH clearance		Initial volume		IVH clearance	
Day	Pearson	*p*	Pearson	*p*	Pearson	*p*	Pearson	*p*	Pearson	*p*	Pearson	*p*
1	0.03	0.707	0.11	0.24	0.15	0.37	0.02	0.91	−0.15	0.12	0.11	0.27
2	0.19	0.003	0.12	0.07	0.09	0.37	0.13	0.22	0.04	0.51	−0.07	0.32
3	0.23	<0.0001	0.21	<0.0001	0.12	0.18	0.23	0.01	−0.06	0.06	0.002	0.97
4	0.25	<0.0001	0.14	0.008	0.24	0.007	0.17	0.06	−0.04	0.45	0.13	0.02
5	0.27	<0.0001	0.10	0.06	0.24	0.003	0.12	0.15	0.01	0.82	0.03	0.58
6	0.29	<0.0001	0.04	0.45	0.40	<0.0001	0.05	0.56	0.02	0.76	0.11	0.08
7	0.29	<0.0001	0.06	0.37	0.34	<0.0001	−0.03	0.77	−0.08	0.21	0.11	0.08
8	0.28	<0.0001	−0.05	0.52	0.25	0.02	−0.09	0.43	−0.08	0.31	0.02	0.75
9	0.35	<0.0001	−0.06	0.56	0.46	0.0001	−0.04	0.77	−0.08	0.45	0.1	0.37
Mean	0.35	<0.0001	0.11	0.02	0.30	<0.0001	0.10	0.07	−0.02	0.23	0.08	<0.0001
Median	0.18	<0.0001	0.13	<0.0001	0.08	<0.0001	0.09	<0.0001	−0.05	0.01	0.1	<0.0001
Maximum	0.19	<0.0001	0.12	<0.0001	0.19	<0.0001	0.10	<0.0001	−0.02	0.19	0.1	0.0001

characterize the outcome measures. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC). Graphs were plotted by GraphPad Prism 6.0 (GraphPad Software Inc., La Jolla, CA). *p* Values were 2-sided and considered statistically significant at $p < 0.05$.

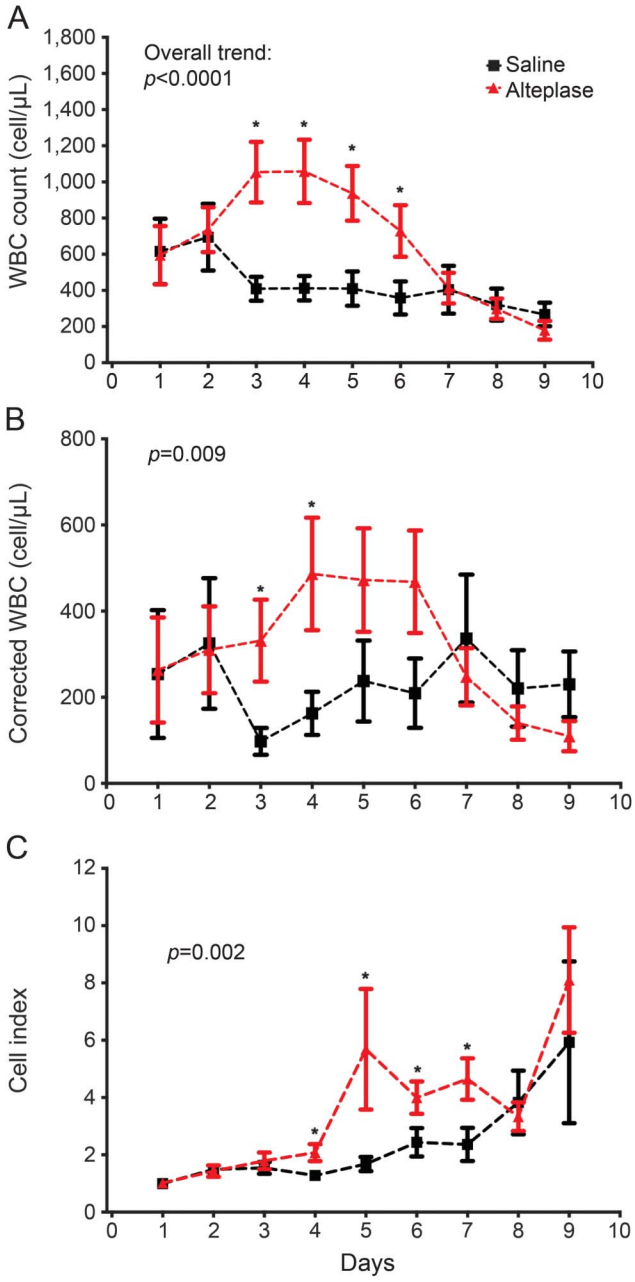
RESULTS The overall temporal trends (figure 1) show an early, modest elevation in CSF WBC at days 1–3 parallel to a similar increase of CSF RBCs. After the third day, RBC counts decrease with a slower rate of WBC decline. This gap between the 2 slopes of RBC and WBC declines starting on the third day and coincides with a delayed surge in cWBC and a rise in CI. CSF protein levels fall steeply from onset to day 2, with a more gradual decrease thereafter, and CSF glucose shows very little fluctuation between 70 and 80 mg/dL throughout days 1–9 (figure e-1A).

Effect of iIVH volume and IVH clearance. There were greater CSF WBC and protein in cases with higher iIVH (figures 2 and e-1B). A higher CSF WBC response was appreciated in cases with iIVH exceeding 20 mL ($p < 0.0001$); however, the difference between the 2 higher volume strata (20–50 and >50 mL) was less evident ($p = 0.06$). A similar pattern was noted with cWBC, while CI exhibited a similar trend but no differences in the 3 volume strata (figure 2). CSF glucose showed a similar but inverse correlation with iIVH, with levels lower in cases with iIVH volumes exceeding 20 mL (figure e-1B). iIVH and IVH clearance, considered as respective continuous variables, showed positive correlations with CSF WBC counts on days 2–9. Similar correlations were seen with cWBC but not CI. In per-patient analysis, iIVH demonstrated a strong positive correlation with mean, median, and maximum WBC and cWBC ($p < 0.0001$). CI, on the other hand, showed no relationship with iIVH but correlated positively with IVH clearance (on day 4, and mean, median, and maximum per participant) (table 1).

Effect of thrombolytic treatment. Participants receiving the alteplase group had consistently higher CSF WBC ($p < 0.0001$), cWBC ($p = 0.009$), CI ($p = 0.002$), and protein ($p < 0.0001$), and lower CSF glucose ($p = 0.0003$), compared to participants receiving saline (figures 3 and e-1C). We queried the effect of alteplase using a general linear model adjusting for iIVH volumes. Compared to saline, alteplase was associated with greater CSF inflammatory response as demonstrated by mean, median, and maximum CSF WBC, cWBC, and CI, independent of iIVH volume (tables e-4–e-6).

Effect of bacterial infection. Participants with positive CSF bacterial culture during the sampling protocol (days 1–10, n = 21) were analyzed in comparison to the remaining cohort (figure 4). The overall trends of CSF measures confirmed that even in the context of IVH, cases with CSF infection have a higher CSF WBC ($p = 0.03$) and protein ($p = 0.03$) and lower glucose levels ($p < 0.001$). This distinction was lost when correcting for blood in CSF using cWBC ($p = 0.79$) and CI ($p = 0.11$). Per-patient analysis of CSF WBC expressed as mean, median, or maximum values showed a strong association with bacterial infection ($p = 0.002$, $p < 0.001$, and $p = 0.003$, respectively). A similar correlation was evident with CI but not

Figure 3 Association of thrombolytic treatment



Temporal trend CSF white blood cells (WBC), corrected WBC, and cell index in cases with alteplase vs saline administered via external ventricular drain over days 1–9 postictus. The *p* value listed with each panel refers to the difference in overall trend for the respective measure. *Refers to significantly different daily values.

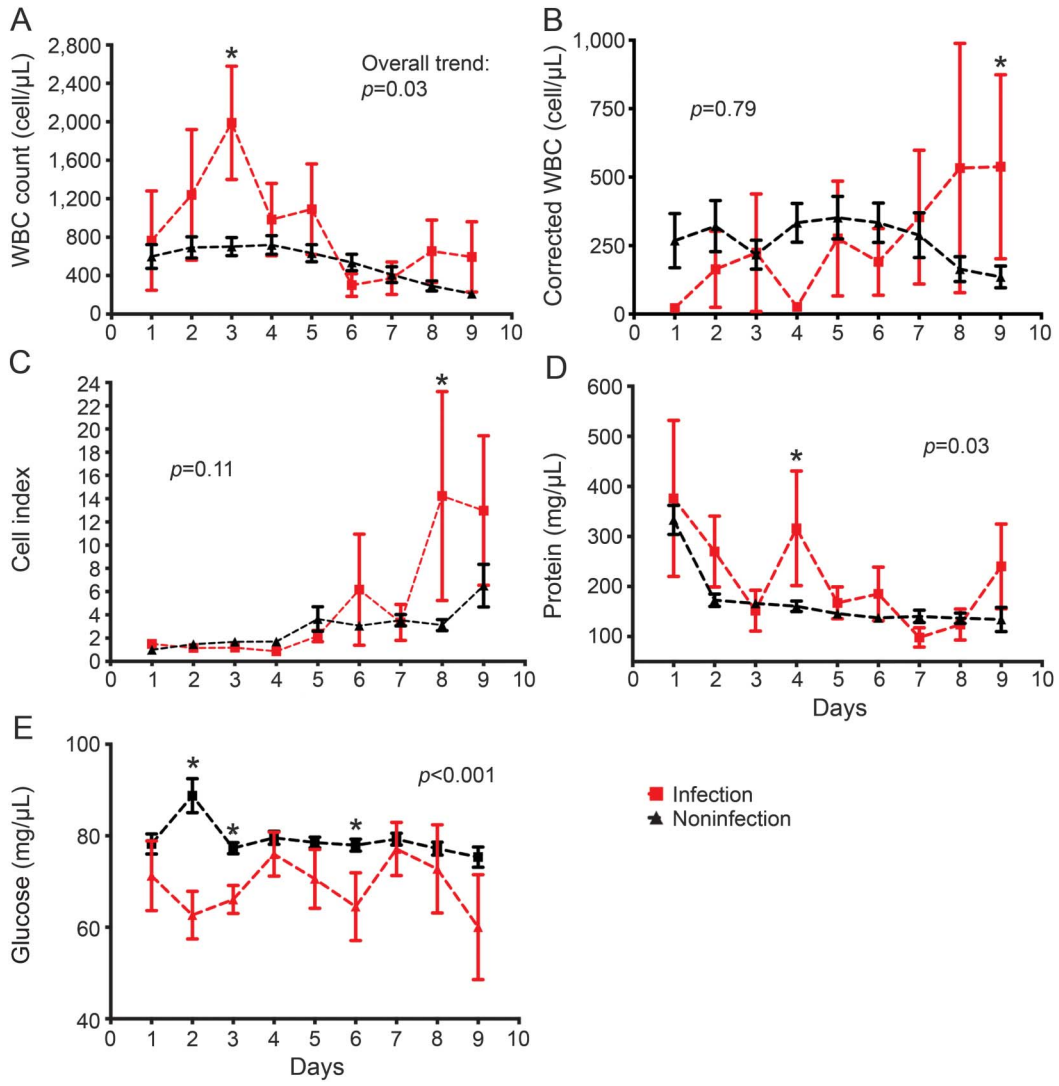
cWBC (table e-7). There was no predictive trend of CSF inflammatory response preceding the time of sample with first positive culture (figure e-2). Extending the analysis to cases with CSF-positive culture within 30 days (n = 31) showed a weaker correlation with CSF inflammatory response assessed in days 1–9 (figure e-3).

CSF inflammatory response and clinical outcome. No correlation was found between the CSF inflammatory measures (WBC, cWBC, and CI) and poor functional outcome (mRS 4–6) or mortality at 30 or 180 days (tables e-8 and e-9). General linear model of 30- and 180-day outcomes confirmed that no measure of CSF inflammation (mean, median, or maximum CSF WBC counts, cWBC, or CI) had a significant association with poor outcome or mortality after correction for prognostic indicators in the CLEAR III trial (iIVH volume, IVH clearance, ICH volume, thalamic/nonthalamic ICH location, and GCS at presentation) (tables e-10 and e-11). There was a marginal correlation ($p = 0.05$) of median CI during days 1–9 with mRS 4–6 at 30 but not 180 days.

IVH participants with highest inflammatory response. The upper quartile of participants based on CSF WBC, representing the group with strongest inflammation, did not exhibit any notable difference in baseline demographic features or medical history compared to the remaining CLEAR III participants, except for slightly higher female preponderance. The clinical management in the 2 groups was effectively similar in terms of timing of EVD insertion, initiation, duration, and frequency of dosing. However, patients with higher inflammatory response had lower GCS at presentation ($p = 0.02$); this group also had higher iIVH volumes ($p = 0.0006$). A greater fraction of patients in the high inflammation cohort received alteplase (67.2% vs 44.8%, odds ratio 2.4, confidence interval 1.63–3.93; $p = 0.0067$) and achieved higher IVH clearance (79% vs 40.2%, odds ratio 5.9, confidence interval 3.59–9.83; $p < 0.0001$). Participants with highest inflammatory response also required longer EVD time and intensive care unit stay. Despite the greater disease severity, no difference in 30- or 180-day functional outcome or mortality was seen in this group (table e-12). Similar results were noted when considering cWBC and CI upper quartiles for definition of the high inflammation group (tables e-13 and e-14).

DISCUSSION We investigated classic CSF measures for the time course of inflammatory response and relevant associations in participants in the CLEAR III trial. This represents the largest prospectively enrolled cohort with IVH compiled to date, with systematic sampling of CSF and adjudicated measurements of IVH volume and clinical outcome. Our results demonstrate that an aseptic CSF inflammation is a normal response in the days following IVH. Greater extent of inflammatory response was present in cases with higher iIVH volume, most evidenced by early elevated WBC at days 2–3, slightly later cWBC elevation at days 4–5, and a lesser extent of elevated CI, accompanied by decreased CSF glucose and gradually decreasing CSF protein. The CSF inflammatory response was more pronounced in cases with higher

Figure 4 Association of bacterial infection



Temporal trend of CSF (A) white blood cells (WBC), (B) corrected WBC, (C) cell index, (D) protein, and (E) glucose during days 1–9 postictus in cases with and without bacterial infection manifested during the study period (within 10 days postictus, n = 21). The *p* value listed with each panel refers to the difference in overall trend for the respective measure. *Refers to significantly different daily values − daily value $p < 0.05$.

IVH clearance, mostly illustrated by uncorrected WBC counts. This could be partly due to the release of hemorrhage-driven leukocytes trapped in the clot or to proinflammatory effects of clot degradation products. It is also possible that cases with lower IVH clearance had a more delayed inflammation that was not observed in days 1–9 of CSF sampling in our study.

Intraventricular thrombolytic therapy was associated with a surge in CSF pleocytosis that was independent of IVH volume and clearance rate. All prior studies to date of CSF inflammatory measures after hemorrhagic stroke represented single site case series, with potential selection biases, and few examined IVH specifically (table e-15). While the general trend of CSF inflammatory measures is noted in several reports, none was powered to examine effects of IVH volume or clearance rates, and none presented any meaningful correlations with clinical outcome. Only one study examined the effect of thrombolysis with appropriate randomized controls, but it included only 12 participants.[14] This study, along with another one,[14,15] suggested proinflammatory properties of thrombolytic drug consistent with our results.

The CSF pleocytosis did not independently affect mortality or functional outcome. No measure of CSF inflammation (daily, mean, median, or maximum sampled values) correlated with functional outcome or mortality with or without controlling for iIVH volume, IVH clearance, or thrombolytic treatment. Despite their greater disease severity (larger iIVH and lower GCS score), no difference in long-term

functional outcome or mortality was seen in patients with the most severe cases of CSF inflammation. This suggests a compensatory clinical benefit of greater clearance rates and thrombolytic therapy. Such benefit of thrombolysis and greater IVH clearance was indeed documented in the trial in the subgroup of cases with large volume IVH.[19] These results do not exclude more subtle sequelae of inflammatory response not measured by mRS at 30 and 180 days. It remains possible that modulation of the inflammatory response, including the use of steroids or nonsteroidal anti-inflammatory agents, could potentially further enhance the benefits of thrombolytic therapy. Our study lacked information on CSF neutrophils vs monocyte pleocytosis, and did not examine cytokines or other measures that could be more sensitive markers of harmful or beneficial impact. Other reports have indeed correlated peripheral blood monocyte counts with untoward outcome after hemorrhagic stroke,[25–27] but we are unaware of specific studies addressing IVH or examining CSF cell types.

Changes in the CSF picture in association with bacterial infection have been well described in the diagnosis of meningitis/ventriculitis.[11,28,29] Yet blood contamination of the CSF can also mask a true septic response. Cases with culture-positive CSF infection diagnosed during the course of CSF sampling had higher pleocytosis and protein and lower glucose. Adjustment using cWBC or CI at least partially eliminated the difference observed in uncorrected WBC. Our findings support the previous reports on the tendency of these measures (cWBC and CI) to overcorrect and thereby potentially mask a true infection.[20,22] From a practical perspective, there were no inflammatory measures predictive of infection in the setting of IVH, hence there is no substitute to culturing CSF frequently in order to exclude infection, especially in cases with greater CSF pleocytosis or lower glucose levels.

Our study had several other limitations. There were missing data resulting from sites failing to report daily CSF results as per trial protocol. The effect of missing data was mitigated by comparison of cases with and without missing data, by randomized treatment assignment, and by adjudicated outcome assessment unrelated to the sampling of CSF measures. The absence of mandated daily CSF cultures and the frequent use of antibiotic prophylaxis may have confounded the detection of true infection and its correlation with classic CSF measures. The relationship of CSF inflammatory markers to fever and systemic and neurologic adverse events was not addressed herein, and is being examined in separate analyses beyond the scope of this report. Factors associated with permanent CSF shunting in the CLEAR III trial were addressed in another recent publication.[30]

AUTHOR CONTRIBUTIONS

All authors were involved in the concept, design, drafting, and critical revision of the manuscript. D.H. and I.A.A. co-chaired the CLEAR trial and supervised patient screening and enrollment. M.D.F., J.K.E., S.J., D. F.H., W.Z., and I.A.A. were involved in study conceptualization, hypothesis, and study design. M.D.F., J.K.E., N.M., K.L., A.S., H.A. Z., and M.J. were involved in data collection, analysis, and interpretation of results. Y.C., M.W., R.E.T., and L.Z. contributed to the statistical analysis. M.D.F., H.A.Z., and J.K.E. were responsible for writing the manuscript with supervision by I.A.A. and for preparing tables, panels, and figures.

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DISCLOSURE

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